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Paravalvular leakage after mitral valve replacement: improved long-term survival with aggressive surgery?[☆]

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Abstract

Background: Following mitral valve replacement, surgical closure of paravalvular leaks is usually advised in severely symptomatic patients and in those requiring blood transfusions for persisting haemolysis. However, the long-term prognosis of less symptomatic patients or those not needing blood transfusions is unknown. **Methods:** Between 1987 and 1997, we observed 96 patients with mitral paravalvular leakage. A paraprosthesis leak was diagnosed after a median time of 119 days (range: 1 day–23 years) after primary mitral valve replacement. During an average follow-up of 5 years (range: 1–23 years), 50/96 patients were referred for surgical closure. **Results:** Compared with patients who received conservative treatment, those referred for surgery had a significantly lower mean preoperative haematocrit ($P = 0.002$) with a higher proportion of patients being in the NYHA class III/IV ($P = 0.03$). Age, gender, left ventricular function and number and size of leaks did not differ between the groups. The 30-day postoperative mortality for valve reoperation was 6% (3/50); during follow-up three further patients died, resulting in an overall mortality rate of 12%. In the group treated conservatively there was a mortality rate of 26% (12/46). Thus, the actuarial survival for patients referred for surgery was 98, 90 and 88% after 1, 5 and 10 years, compared with 90, 75 and 68% for patients treated conservatively (long-rank $P = 0.03$). In addition, there was a significant increase in mean haematocrit levels ($P = 0.0001$) and an improvement in NYHA class III/IV symptoms ($P = 0.002$), vertigo ($P = 0.001$) and fatigue ($P = 0.001$) after surgery. **Conclusions:** Following mitral valve replacement, a more aggressive surgical treatment is recommended for patients with paraprosthesis leaks. Surgery should be offered to less symptomatic patients, as well as those not requiring blood transfusion. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Surgery; Mitral valve replacement; Paravalvular leaks; Survival

1. Introduction

Cardiac valve replacement is a well-established and safe procedure with a low mortality rate. It confers considerable benefits in patients with chronic valvular disease in terms of improved cardiac physiological function and increased survival. The procedure is not, however, free from complications, such as thromboembolism, anticoagulant-related haemorrhage, prosthetic valve endocarditis and valve dysfunction.

Valve dysfunction may be caused by a variety of factors, including infection, tissue failure associated with bioprostheses or mechanical problems. Recurrent regurgitation,

which may be due to a paraprosthesis leak, is a clinical manifestation of valve dysfunction and may itself arise from a variety of causes. Surgical closure of paravalvular leaks is usually advised in severely symptomatic patients and in those requiring blood transfusions for persisting haemolysis. However, the long-term prognosis of less symptomatic patients, or those not needing blood transfusions, is unknown.

2. Patients and methods

A new holosystolic regurgitant murmur is an indication of the presence of a paravalvular leak. The gold standard procedure for diagnosis of a paravalvular leak in the mitral position is echocardiography [1–3]. Optimal visualization of mitral jets, and the absence of acoustic shadowing from prosthetic material in the left atrium, account for the

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increasing use of trans-oesophageal echocardiography in evaluating mitral prostheses. Nowadays, however, the use of be-leaflet mechanical prostheses means that the diagnosis is no longer simple. These prostheses characteristically have two to four small, low turbulence jets originating from within the valve ring. Regurgitation is considered to be paravalvular if a turbulent eccentric jet originates outside the prosthetic sewing ring, or a paravalvular gap is visualized between the annulus and the sewing ring. The pathology of the mitral valve is summarized in Fig. 1.

Between 1987 and 1997, 618 mitral valve replacements were performed at the University Hospital in Zurich. In this series, we observed 82 paravalvular leaks in 75 patients (primary leaks in 75 patients in 598 operations and seven re-leaks in 20 reoperations). A further 21 patients with mitral paravalvular leak, in whom primary mitral valve replacement was performed either before 1987 or at another institution, were surgically treated during the same observation period. In total, 49/96 patients (51%) were male and 47/96 (49%) were female. The mean age at the time of the mitral valve replacement that caused the leak was 54.6 years (± 13.4 ; range 25–80 years).

All patients underwent standard cardiopulmonary bypass with arterial and bicaval (45%) or atrial (55%) cannulation. Cardioplegia and systemic hypothermia were used to protect the myocardium in 68% of patients, whilst in the remaining 32%, surgery was performed in ventricular fibrillation. The surgical technique employed for primary mitral valve replacement included complete excision of valve tissue in 69% and conservation of the posterior leaflet in

31%. The mitral prosthesis was customarily secured by interrupted sutures of 2/0 Ticron. A mechanical prosthesis was used in 97% of cases. Patients with mechanical prostheses received anticoagulant treatment with warfarin from the first postoperative day. All patients received antibiotics at induction of anaesthesia and post-operatively for 24 h; antibiotic treatment was prolonged in some patients where clinically indicated.

Records of all patients with mitral paravalvular leak were reviewed. All patients who were still alive were contacted and asked to complete a questionnaire with the help of their doctor (in particular for the echocardiography data). The total follow-up period covered 517 years, with a mean observation time of 5.17 years. A total of 18/96 (19%) patients died during the follow-up period; of the remaining 78 patients, follow-up was completed in 72 (92%).

2.1. Statistical analyses

Distribution for all relevant variables was reported either as a percentage or as the mean \pm standard deviation. Statistical analyses were performed using the SPSS 6.1 program. The effects of nominal risk factors were evaluated with the Chi-quadrant test. The effects of independent variables were evaluated with the Mann–Whitney and Kruskal–Wallis tests; continuous variables were univariately evaluated with the Wilcoxon-signed rank test. Differences between groups were analyzed using the log rank test and Cox-regression was used to detect independent risk factors. Significance was assumed at a *P*-level of < 0.05 .

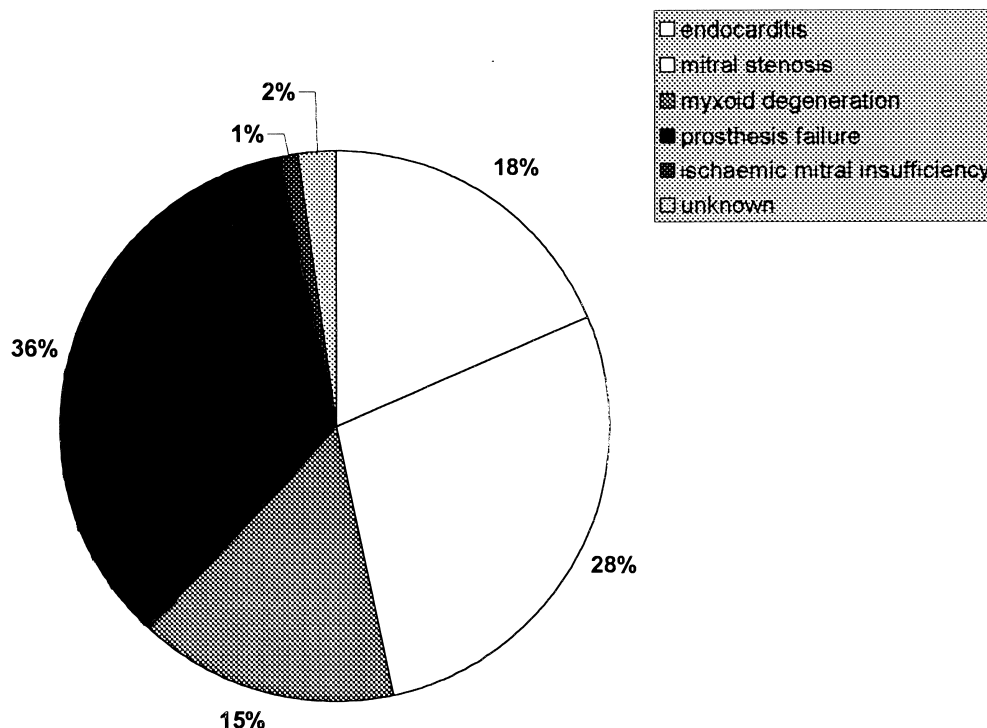


Fig. 1. Pathology of mitral valve disease.

Table 1

Incidence of paravalvular leak in subgroups of patients with different underlying diseases

	Mitral valve replacement	Paravalvular leak	Incidence (%)
Mitral valve replacement reoperation	260	32	12.3
Mitral stenosis	84	10	11.9
Mitral valve prolapse	62	11	17.7
Combined mitral valve disease	150	13	8.6
Ischaemic mitral valve regurgitation	24	1	4.7
Endocarditis	29	12	41.4
Paravalvular leak ('re-leak')	20	7	35

3. Results

The incidence of primary paravalvular leak after mitral valve replacement in patients who underwent surgery during the same time period at the same institution was 12.5% (75/598). As shown in Table 1, the incidence of paravalvular leaks differed between subgroups of patients with different underlying diseases; the risk was highest after mitral valve replacement for mitral valve endocarditis and re-leak.

Symptoms at the time of diagnosis of paravalvular leak after mitral valve replacement were major fatigue (67% of patients), vertigo (55%) and NYHA class III/IV dyspnoea (38%). Only 12.5% of patients had heart failure.

The interval between mitral valve replacement and diagnosis of a paravalvular leak was 798 days (± 1674 days; median 119 days). The longest period between mitral valve replacement and the diagnosis of paravalvular leak was 23 years. Fig. 2 shows the number of diagnoses during different time intervals after mitral valve replacement; 74% of paravalvular leaks were diagnosed during the first post-

operative year and 22% during the first postoperative week. Significant predictors for a shorter interval between mitral valve replacement and diagnosis of paravalvular leak were older age ($P = 0.01$), surgeons with less experience of mitral valve prostheses ($P = 0.019$), larger leaks ($P = 0.023$) and extended haemolysis ($P = 0.001$).

The 96 patients were divided in two groups; 46 were treated conservatively and 50 were treated surgically. The decision to reoperate was mainly influenced by the cardiologists' referral practice. Their decision to refer the patient to the surgeons was based on the normal indications for surgery. They could, upon follow-up examination, transfer any of the patients to the surgical group. Comparison of the baseline data for these two groups revealed significant differences in terms of NYHA class III/IV symptoms, haematocrit and lactate dehydrogenase (LDH) levels (Table 2). Highly symptomatic patients were more frequently treated surgically; 80% of the patients with NYHA class III symptoms and 67% with NYHA class IV symptoms were included in the surgical group (Fig. 3). The surgically treated patients also had more marked haemolysis (Fig. 4) resulting in a significantly higher LDH level and a significantly lower haematocrit.

The early mortality in the surgical group was 6% ($n = 3$). During the whole observation period there were 12 deaths in the conservative group, three of which were valve-related, resulting in a mortality rate of 26%. In the surgically treated patients, there were six deaths in total, resulting in an overall mortality of 12%. Statistical analysis of survival using the Cox-regression model (Fig. 4) revealed a significantly better survival after surgery ($P = 0.035$).

Surgery not only improved survival, but also the symptoms. Table 3 shows the significant improvement in symptoms (NYHA class III/IV, $P = 0.002$; vertigo, $P = 0.001$; and fatigue, $P = 0.001$) and haematocrit ($P = 0.001$) at follow-up in surgically treated patients. Moreover, the conservatively treated patients needed significantly more blood transfusions ($P = 0.05$).

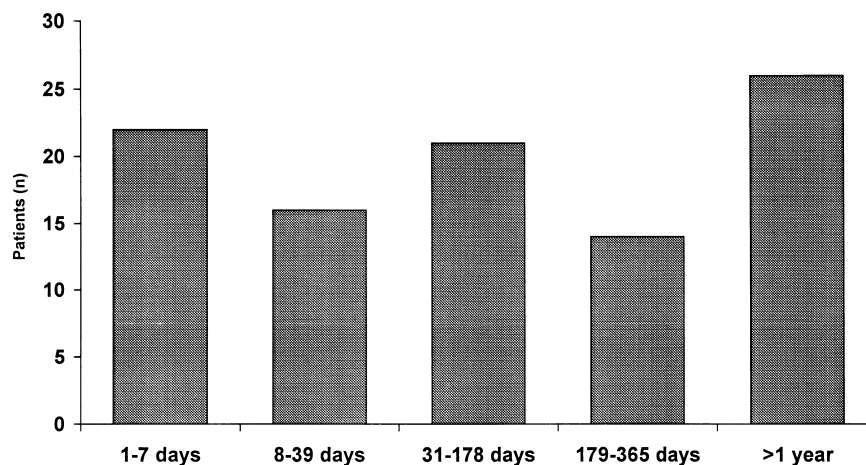


Fig. 2. Interval between mitral valve replacement and diagnosis of paravalvular leak.

Table 2

Comparison of baseline data between surgically and conservatively treated patients

	P-value
Age	ns
Gender	ns
Size of leak	ns
Localization of leak	ns
Number of leaks	ns
Atrial size	ns
Fatigue	ns
Vertigo	ns
Interval between mitral valve replacement and diagnosis	ns
Underlying disease	ns
Coronary artery disease	ns
Diabetes mellitus	ns
Renal insufficiency	ns
Calcification of the mitral valve annulus	ns
NYHA class III/IV symptoms	0.029
Haematocrit	0.0016
LDH	0.0017

The procedures carried out in the surgically treated group included the reattachment of the prosthesis with interrupted sutures in 30/50 patients (60%) and replacement of the mitral prosthesis in 20/50 patients (40%). Re-leak after surgical closure of the primary mitral paravalvular leak was found in 11/50 patients (22%). No risk factors for the development of a re-leak were identified; four cases occurred after reattachment and seven after mitral valve replacement ($P = 0.74$), this indicating no influence of surgical procedure.

4. Discussion

Despite an operative mortality of 6%, surgery offers improved survival and a reduction in symptoms in patients with paravalvular leak after mitral valve replacement. For

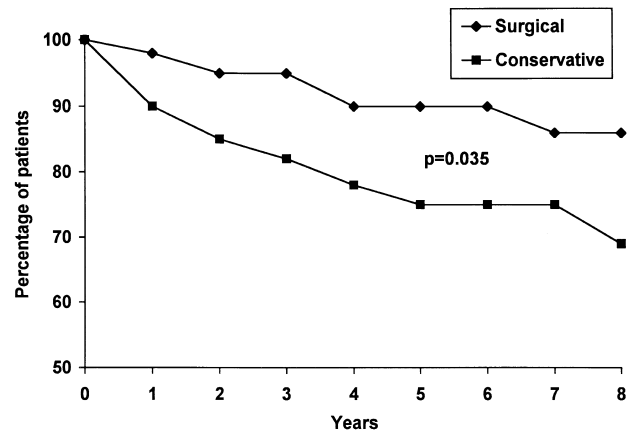


Fig. 4. Influence of therapeutic strategy on survival.

these reasons, surgery should be offered to less symptomatic patients, as well as those not requiring blood transfusion.

The incidence of paravalvular leak after mitral valve replacement was 12.5%; this does not include paravalvular leaks identified accurately at the time of surgery by intra-operative transoesophageal echocardiography. This rate corresponds to that reported by other authors [4–6]. Some reports of lower rates are explainable by the selection of the patients. For example, Dhasmana [5] reported an incidence of 9.3%, but excluded all patients with endocarditis as the underlying reason for mitral valve replacement. This is especially notable, as endocarditis was associated with the highest incidence of paravalvular leak in our study. The development of a paravalvular leak in the early postoperative period in a patient with infective endocarditis, or sustained positive blood cultures despite adequate antibiotic therapy, indicates a failure to control the infection [7]. In these cases, prolonged antibiotic therapy is necessary following diagnosis of the leak and prior to surgery. However, the majority of late paravalvular leaks are not associated with recurrent infection and can be repaired with-

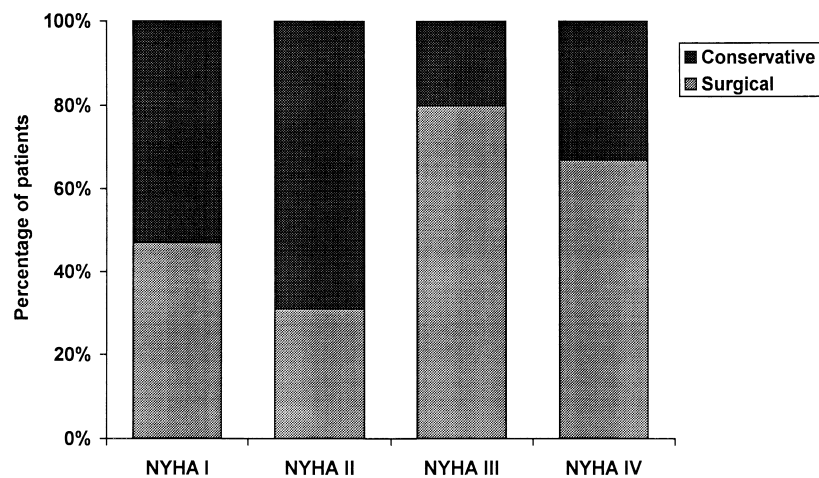


Fig. 3. Comparison of pre-operative NYHA functional status between surgical and conservative strategies.

Table 3

Incidence of symptoms, haematocrit and requirement for transfusion at follow-up

		Surgical treatment (%) ^a	Conservative treatment (%)	P-value
NYHA class III/IV	Follow-up	26	21	0.51
	At diagnosis	61 (0.002)	15	–
Vertigo	Follow-up	34	56	0.06
	At diagnosis	50 (0.001)	56	–
Fatigue	Follow-up	45	68	0.15
	At diagnosis	64 (0.001)	69	–
Haematocrit	Follow-up	42	37	0.29
	At diagnosis	31 (0.001)	34	–
Transfusion	Follow-up	6	15	0.05

^a Figures in parentheses represent P-values.

out replacement of the valve. For example, in the Stanford series [8], five of six patients with late paravalvular leak had an annular abscess at initial surgery.

Due to the very strictly controlled indication for bioprosthesis in the mitral position in our institution [9], we can not verify the statement of Hammermeister [10], who reported a lower incidence of paravalvular leaks after bioprosthesis in contrast to von Segesser [9]. Dhasmana [5] also suggested that the use of a small monofilament suture in a continuous suture technique may be another contributory factor in the development of a paravalvular leak. In all cases, we used an interrupted pledgeted 2-0 Ticron mattress suture technique.

The underlying disease of the mitral valve does not influence the interval between mitral valve replacement and diagnosis of paravalvular leak. In our study, the median interval of 119 days between replacement and diagnosis was smaller than that reported in other publications. This could be the consequence of accurate follow-ups by our cardiologists at 3 months and 1 year postoperatively. It is interesting to note the influence of the age of the patient, the size of the leak and extended hemolysis on this interval.

Paravalvular leaks are the most common reason for repeat of mitral valve replacement surgery [7,11,12]. Amongst the 75 patients with paravalvular leaks after mitral valve replacement performed at our institution between 1987 and 1997, 29 (39%) had surgical treatment.

Compared to Jindani [4], who reported a mortality rate of 22% following reoperation, our early mortality is markedly lower and confirmed the opinion of Syracuse [13], who considered reoperation for paravalvular leaks to be a low-risk operation. In our study, we can show that surgical strategies are associated with better survival than conservative strategies. The baseline data at the time of diagnosis of the paravalvular leak were comparable for the two groups, with the exception of more NYHA class III/IV symptomatic patients and more extended haemolysis in the surgical group. The decision as to which treatment strategy the patients received was made by the cardiologist. Surgery is clearly indicated in patients requiring blood transfusion and those with signs of heart failure [4]. Although there is nowadays widespread agreement among cardiologists and

surgeons alike that severe paravalvular leak should be corrected immediately, the management of patients with mild and moderate paravalvular leak is controversial. Movsowitz [2] reported clinical deterioration over time in some patients with moderate and mild leaks. The number and size of the leaks was not a criterion for choosing a surgical strategy. However, we saw that larger leaks resulted in more dyspnoea and multiple leaks resulted in extended hemolysis; thus, the characteristics of the leaks may have indirectly influenced the decision. Despite the fact that surgically treated patients are at an overall higher risk, the mortality rate in the follow-up period was significantly lower than in conservatively treated patients. The consequence of this finding is that surgical treatment must also be guaranteed in patients who are less symptomatic and in those not requiring blood transfusion. Not only was the mortality rate lower, but the symptoms were also reduced to a lower level than seen in the conservatively treated group. In addition, surgery decreased the need for blood transfusion during the follow-up period.

Delay of surgery may increase the mortality rate. Indeed, in the series of Jindani [4], the interval between mitral valve replacement and diagnosis of the paravalvular leak was longer, the number of patients with heart failure was higher and the mortality rate was higher. Nevertheless, patients undergoing reoperation of primary tissue failure of the prosthesis have been reported to have a better life expectancy compared with those having reoperation because of paravalvular leak, endocarditis or thrombosis [14].

The surgical procedures used comprised either reattachment of the valve with single stitches or a mitral valve replacement. In cases of intermediate and large paravalvular leaks, valve replacement was preferred. We did not observe any differences between these two procedures in terms of symptoms, haemolysis or left ventricular function. The choice of technique should therefore be surgeon-dependent.

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Appendix A. Conference discussion

Dr M. Antunes (Coimbra, Portugal): Weren't your results a little bit skewed by the fact that there were indeed some patients who required blood transfusions, for example, in the conservative group. If those patients had been removed from the conservative group and treated surgically, would not the differences be less evident?

Dr Genoni: The difference is that in the surgery we started our observation time at the time when the diagnosis of paravalvular leak was made. Then we divided the patients in the surgical and in the conservative group.

So the patients in the conservative group have a follow-up time of 5 years, and in these 5 years they receive blood transfusions.

Dr J. Bachet (Paris, France): Paravalvular leaks after surgery obviously call the surgical technique into play. Could you give us some details on how you implant the mitral valve and what kind of technique you use? Do you use a continuous suture, interrupted suture, or pledgeted sutures, etc?

Dr Genoni: All the primary mitral valve replacements were inserted with an interrupted pledgeted suture technique.

Dr Antunes: It is interesting, because the incidence, which we know is much larger than one usually believes, was 12.5%, and it is usually believed that it is much less with interrupted sutures.

Dr Genoni: Yes, but I think the incidence is the same as reported in the literature.

Dr Antunes: I am not arguing with that.

Dr Genoni: Because you find only a few reports including all patients.

Dr R. Autschbach (Leipzig, Germany): Can you tell us something about the valves you implanted and the sizes of these valves?

Dr Genoni: No, the sizes I don't know right now, but in 96% of our patients we used mechanical valves and in 4% we used biological valves.

Dr H. Oelert (Mainz, Germany): When you closed the paravalvular leak, was it always possible to close the leak or do you also have to rereplace the valve? In our experience, especially if there is endocarditis as the basic lesion, you should replace the valve instead of repairing a leak.

Dr Genoni: Well, the procedure carried out in the surgically treated group was reattachment of the prosthesis in 30 out of 50 patients, which was 60%, and replacement in 40% of our patients. We observed in this retrospective study that patients with a small leak were mainly reattached, and those with large and multiple leaks were subjected to replacements. The patients with large leaks are also those that had endocarditis at primary mitral valve replacement.

Dr Antunes: Were they still infected at the time of the closure of the paravalvular leak? Could you correlate with that?

Dr Genoni: Only 10% of the patients with endocarditis had primary mitral valve replacement.

Dr G. Rizzoli (Padova, Italy): I would like to know how your patients were stratified between surgery and conservative treatment, and especially what was the crossover rate of patients from the medical to the surgical treatment? Also I would like to know why about 70% of your patients in the third and fourth class have been operated on? What happened to the remaining 30%?

Dr Genoni: The problems faced by patients is that they are examined by cardiologists, and the cardiologists, in turn, have to decide whether to refer the patients to surgeons. We only saw the patients in our retrospective study. Our current policy is that we operate on all patients that are symptomatic, all patients with hemolysis. We only wait for the operation on patients with a small leak, patients with solitary leaks and patients with small left atria with normal pulmonary artery pressures. All other patients will be operated on.

Dr F. Wellens (Aalst, Belgium): In this pathology, the challenge for the cardiac surgeon is not the first redo operation, it is the second or the third or the fourth redo operation, leading to a very conservative approach in treating these patients to repair a recurrent leak. Application of Heartport technology for this very difficult subset of patients is excellent, just using the Endoclamp and then making a normal right lateral thoracotomy gives excellent results with very low mortality and morbidity in this difficult subset of patients with recurrent paravalvular leaks.

Dr Antunes: Well, we mustn't forget that this was a retrospective study and that you found what you found.